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Evaluation of the human research act: analysis of the quality of selected human research projects

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Evaluation of the Human Research Act: Analysis of the quality of selected human research projects

Synthesis report

Commissioned by the Federal Office of Public Health (FOPH)

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Summary

Evaluation of the Human Research Act (HRA) that has been in force since 2014

The Human Research Act (HRA) and its associated ordinances have been in force since 2014. Next to its primary aim of protecting human beings in research, it also aims at ensuring the quality and transparency of research involving human beings as well as creating favourable conditions for such research. In federal Switzerland, cantonal ethics committees (ECs) are responsible for authorising human research projects (HRPs). Depending on the type of the project, approval of the Swiss Agency for Therapeutic Products (Swissmedic) or the Federal Office of Public Health (FOPH) may also be required.

In order to assess the effectiveness of the newly introduced HRA and to identify potential for improvement, the FOPH has commissioned the Department of Political Science at the University of Zurich (IPZ) and KEK-CDC Consultants to evaluate the HRA. The evaluation of the HRA relies on diverse methods and integrates the perspectives of the different stakeholders in research involving human beings. It also set out to analyse the quality of research activities subject to the HRA. Due to time constraints and the complexity of this analysis, it had to be separated from the evaluation.

Analysis of the quality of selected human research projects (HRPs) by external specialists

The exploratory analysis of the quality of HRPs focuses on 13 selected projects that have been submitted to the EC in 2016. Its aim is to obtain qualitative assessments of the diverse research activities subject to the HRA. This is why HRPs from the eight most frequent study types and all seven ECs were analysed. Consequently, the HRPs analysed are subject to the Clinical Trials Ordinance (ClinO) or the Human Research Ordinance (HRO). Dealing with diverse research topics, the HRPs analysed were mostly initiated by the investigators, but the analysis also covers HRPs initiated by the industry or third parties. It needs to be considered that in 2016, when the HRPs analysed were submitted, a part of the implementation activities of the HRA were still in the process of establishing and improving.ⁱ

In order to ensure a systematic assessment, we developed human research quality criteria on the basis of the Swiss regulations, international guidelines, literature and a discussion with the evaluation's advisory group. The human research quality criteria consist of total eight criteria that are assigned to either a scientific or an ethical dimension. All criteria need to be considered to assess the risks, burdens and benefits associated with an HRP.

We commissioned four external specialists based outside of Switzerland to assess the quality of the individual HRPs selected with respect to the human research quality criteria. The external specialists' assessments are based on the electronic dossiers at the ECs and, if applicable, Swissmedic. Among other documents, the dossiers most importantly contain the study protocol and participant information, but also the authorities' decision letters. The analysis is limited to the authorization procedure until initial approval of the analysed HRPs. Given the sensitivity of the data analysed, the results are solely presented in the form of an overarching synthesis of the individual assessments of the quality of the HRPs.

Largely positive assessment of the HRPs' quality with a few concerns related to the research design

Overall, the analysis shows that the external specialists assess the quality of the 13 selected HRPs largely positive. Regarding most of the analysed HRPs, the external specialists have no or only minor

ⁱ For more information about the implementation activities, see the evaluation of the HRA:

Widmer, Thomas/ Frey, Kathrin/ Eberli, Daniela/ Schläpfer, Basil/ Rickenbacher, Julia (2019): [Evaluation of the Human Research Act \(HRA\). Executive Summary](#). Zurich: Department of Political Science at the University of Zurich and KEK-CDC Consultants.

Widmer, Thomas/ Frey, Kathrin/ Eberli, Daniela/ Schläpfer, Basil/ Rickenbacher, Julia (2019): [Evaluation des Humanforschungsgesetzes \(HFG\). Schlussbericht](#). Zürich: Institut für Politikwissenschaft der Universität Zürich und KEK-CDC Consultants.

concerns with respect to one or few criteria. Most often, the external specialists miss information about the (planned) analyses, and they question whether the HRP will yield reliable results. They also find that the criteria for selecting participants are not always comprehensively documented or that they are too strictly defined. In a few cases, the external specialists miss information about the division of tasks within the HRP. The results further tend to indicate that the documentation primarily contains explanations about planned scientific publications, whereas there is no information on how study participants are to be informed about the study results. Only in single cases, the external specialists have considerable concerns about an HRP. These concerns mostly relate to major shortcomings in the research design, and partly connected to this, the principal investigators' limited expertise in clinical research.

Higher quality of the HRPs initiated by the industry, no differences between study types

Given that 13 HRPs were analysed, we can only make tentative inferences about differences between the HRPs. Generally, the external specialists assess the quality of industry-initiated or international HRPs more positively than the quality of investigator-initiated HRPs. This result is supported by previous government research on the completeness and accuracy of randomized controlled clinical trial study protocols submitted to Swiss ECs in 2012 and 2016.ⁱⁱ Furthermore, even though HRPs subject to the ClinO mostly required approval already prior to the HRA, we observe a few but no systematic differences between the assessments of the quality of HRPs subject to the HRO and the assessments of HRPs subject to the ClinO. One notable difference is that the external specialists only had concerns about the relevance of the research question for HRPs subject to the HRO.

The analysis further confirms the overall positive assessment of the authorities' decisions and their focus on the protection and information of the participants. The external specialists find the ECs' and Swissmedic's decisions largely to be comprehensible and well founded. In line with the legal framework, Swissmedic's comments on the five HRPs that were subject to its approval focused largely on the quality and safety of the therapeutic products used. Regarding the EC, whose authorization was necessary in all the 13 HRPs, the external specialists often describe the comments as fully appropriate or very helpful. However, the external specialists also point to concerns that they have but which are not reflected in the ECs' comments. These concerns refer to the suitability of the research design, the selection criteria and, in one case, the further use of data or material without gathering informed consent of the persons concerned.

Focus on scientific aspects of quality complementary to previous results

Therefore, the results of the analysis of the quality of selected HRPs provide additional insights to the evaluation of the HRA and government research by drawing the attention to the scientific dimension of human research quality. The external specialists expressed still few, but relatively many concerns about criteria of the scientific dimension compared to the criteria of the ethical dimension. The evaluation of the HRA and government research rather highlight the ethical dimension because they clearly indicate a need for improving the information of participants and the transparency of research involving human beings. Still, the present analysis' emphasis on the scientific dimension does not contradict previous results. Rather, the external specialists with an academic background and somewhat circumstantial knowledge of the Swiss regulations may have focused more on scientific aspects. Overall, this analysis thus reveals exploratory findings about the quality of research activities within the HRA and complements approaches and findings of the evaluation of the HRA and government research projects.

ⁱⁱ For the reports of all the government research projects mentioned, see: <https://www.bag.admin.ch/bag/en/home/das-bag/ressort-forschung-evaluation/forschung-im-bag/forschung-biomedizin/ressortforschungsprojekte-humanforschung.html> [as at 19.12.2019].

Zusammenfassung

Evaluation des schweizerischen Humanforschungsgesetzes (HFG), das seit 2014 in Kraft ist

Das Humanforschungsgesetz (HFG) und die dazugehörigen Verordnungen sind seit 2014 in Kraft. Neben dem primären Zweck des Schutzes des Menschen in der Forschung beabsichtigt das HFG auch, günstige Rahmenbedingungen für die Humanforschung zu schaffen und deren Qualität und Transparenz zu gewährleisten. In der föderalistischen Schweiz sind die kantonalen Ethikkommissionen (EK) verantwortlich für die Bewilligung aller Humanforschungsprojekte (HFP). Je nach Art des HFP bedarf es einer zusätzlichen Bewilligung des Schweizerischen Heilmittelinstituts (Swissmedic) oder des Bundesamts für Gesundheit (BAG).

Um die Wirksamkeit des neu erlassenen HFG zu überprüfen und allfälligen Optimierungsbedarf zu identifizieren, beauftragte das BAG das Institut für Politikwissenschaft der Universität Zürich (IPZ) und KEK-CDC Consultants mit der Evaluation des HFG. Gestützt auf diverse Methoden berücksichtigt die Evaluation die verschiedenen Sichtweisen der Beteiligten an der Humanforschung. Ein Ziel der Evaluation war, die Qualität der gemäss HFG bewilligungspflichtigen Forschungsaktivitäten zu analysieren. Aufgrund zeitlicher Einschränkungen und der Komplexität dieser Analyse musste sie aus der Evaluation des HFG ausgelagert werden.

Analyse der Qualität ausgewählter Humanforschungsprojekte (HFP) durch externe Fachpersonen

Die explorative Analyse der Qualität von HFP konzentriert sich auf 13 ausgewählte Projekte, die 2016 bei den EK eingereicht wurden. Ziel der Analyse ist es, qualitative Einschätzungen der vielfältigen Forschungsaktivitäten im Rahmen des HFG zu erhalten. Daher wurden HFP aus allen sieben EK und den acht häufigsten Studientypen analysiert. Entsprechend sind die untersuchten HFP in der Verordnung über klinische Versuche (KlinV) oder der Humanforschungsverordnung (HFV) geregelt und befassen sich mit diversen Themen. Die meisten der untersuchten HFP wurden von den Prüfpersonen initiiert, die Analyse umfasst aber auch von der Industrie oder Dritten initiierte HFP. Es ist zu beachten, dass die untersuchten HFP 2016 eingereicht worden sind, als sich die Umsetzungsaktivitäten zum HFG teilweise erst etablierten und einspielten.ⁱⁱⁱ

Anhand der Rechtsgrundlagen, internationalen Richtlinien, Literatur und einer Diskussion mit der Begleitgruppe der Evaluation haben wir Qualitätskriterien der Humanforschung entwickelt, die eine systematische Beurteilung erlauben. Die Qualitätskriterien umfassen insgesamt acht Kriterien, die entweder einer wissenschaftlichen oder einer ethischen Dimension zugeordnet sind. Alle Kriterien müssen berücksichtigt werden, um die Risiken, Belastungen und Nutzen eines HFP abzuwägen.

Wir haben vier externe Fachpersonen, die nicht in der Schweiz ansässig sind, mit der Analyse der Qualität der ausgewählten HFP anhand der Qualitätskriterien beauftragt. Die externen Fachpersonen bewerteten die Qualität der einzelnen 13 HFP auf Basis der bei den EK und, falls zutreffend, Swissmedic elektronisch verfügbaren Dossiers. Unter anderem beinhalten diese Dossiers namentlich den Studienplan, die Information zuhanden der Forschungsteilnehmenden und die Entscheide der Behörden. Die Analyse ist auf das Verfahren bis zur erstmaligen Bewilligung beschränkt. Aufgrund der Vertraulichkeit der analysierten Daten werden die Resultate in Form einer übergreifenden Synthese der Qualitätsanalysen der einzelnen HFP präsentiert.

ⁱⁱⁱ Siehe die Evaluation des HFG für mehr Informationen zu den Umsetzungsaktivitäten:

Widmer, Thomas/ Frey, Kathrin/ Eberli, Daniela/ Schläpfer, Basil/ Rickenbacher, Julia (2019): Evaluation des Humanforschungsgesetzes (HFG). Executive Summary. Zürich: Institut für Politikwissenschaft der Universität Zürich und KEK-CDC Consultants.

Widmer, Thomas/ Frey, Kathrin/ Eberli, Daniela/ Schläpfer, Basil/ Rickenbacher, Julia (2019): Evaluation des Humanforschungsgesetzes (HFG). Schlussbericht. Zürich: Institut für Politikwissenschaft der Universität Zürich und KEK-CDC Consultants.

Grösstenteils positive Beurteilung der Qualität der HFP, wenige Bedenken zum Forschungsdesign

Insgesamt zeigt die Analyse, dass die externen Fachpersonen die Qualität der 13 ausgewählten HFP überwiegend positiv bewerten. Die externen Fachpersonen äussern bei den meisten der analysierten HFP keine oder nur geringe Bedenken zu einem oder wenigen Qualitätskriterien. Am häufigsten fehlen ihnen Angaben zu den (geplanten) Analysen oder sie stellen in Frage, ob das HFP belastbare Resultate hervorbringen wird. Zudem bemerken sie, dass die Kriterien zur Auswahl der Forschungsteilnehmenden nicht immer nachvollziehbar oder zu strikt definiert sind. In wenigen Fällen fehlen den externen Fachpersonen Angaben über die Arbeitsaufteilung im HFP. Weiter weisen die Resultate tendenziell darauf hin, dass die Unterlagen vor allem Aufschluss über geplante wissenschaftliche Publikationen geben, während Angaben dazu fehlen, wie Forschungsteilnehmende über die Studienergebnisse informiert werden. Nur in einzelnen Fällen äussern die externen Fachpersonen schliesslich wesentliche Bedenken zu einem HFP. Anlass dazu geben erhebliche Schwächen im Forschungsdesign, und teilweise damit verbunden, mangelnde Expertise der Prüfpersonen in klinischer Forschung.

Industrie-initiierte HFP mit besser bewerteter Qualität, keine Unterschiede nach Studientyp

Zumal 13 HFP analysiert worden sind, können wir nur bedingt Schlüsse über Unterschiede zwischen den HFP ziehen. Generell schätzen die externen Fachpersonen die Qualität von Industrie-initiierten oder internationalen HFP deutlich positiver ein als die Qualität von Prüfperson-initiierten HFP. Dieses Ergebnis wird gestützt durch die Ressortforschung zur Vollständigkeit und Genauigkeit von Studienprotokollen für randomisierte kontrollierte klinische Versuche, die 2012 und 2016 bei den Schweizer EK eingereicht worden sind.^{iv} Weiter beobachten wir keine systematischen Unterschiede zwischen den Bewertungen der Qualität der HFP im Bereich der HFV und der KlinV, obschon HFP im Bereich der KlinV zumeist bereits vor Einführung des HFG eine Bewilligung benötigten. Ein bemerkenswerter Unterschied ist aber, dass die externen Fachpersonen die Relevanz der Forschungsfrage nur bei HFP im Bereich der HFV kritisch bewerten.

Die Analyse bestätigt weiter die insgesamt positive Beurteilung der Entscheide der Behörden und ihr Fokus auf den Schutz und die Aufklärung der Forschungsteilnehmenden. Die externen Fachpersonen bewerten die Entscheide von EK und Swissmedic überwiegend als verständlich und fundiert. In Übereinstimmung mit den Rechtsgrundlagen konzentrierte sich Swissmedic bei den fünf von ihr genehmigten HFP vor allem auf die Qualität und Sicherheit der verwendeten Heilmittel. Die Ausführungen der EK, die alle 13 HFP bewilligen mussten, bezeichnen die externen Fachpersonen häufig als angemessen oder sehr hilfreich. Sie weisen jedoch auch darauf hin, dass gewisse ihrer Bedenken nicht in den Ausführungen der EK aufgegriffen werden. Dabei geht es um Fragen zur Eignung des Forschungsdesigns, zu den Auswahlkriterien der Forschungsteilnehmenden und in einem Fall zur Weiterverwendung von bereits gewonnenen Daten oder Material mit Verzicht auf eine Einwilligung der betroffenen Personen.

Fokus auf wissenschaftlichen Aspekten der Qualität ergänzend zu bisherigen Ergebnissen

Die Ergebnisse der Analyse der Qualität ausgewählter HFP lenken folglich die Aufmerksamkeit auf die wissenschaftliche Dimension der Qualität von Humanforschung und erweitern damit die Ergebnisse der Evaluation des HFG und der Ressortforschung. Die externen Fachpersonen haben zwar wenige aber doch relativ häufiger Bedenken zu Qualitätskriterien der wissenschaftlichen Dimension geäussert als zu jenen der ethischen Dimension. Die Evaluation des HFG und die Ressortforschung betonen hingegen die ethische Dimension, indem sie klaren Verbesserungsbedarf bei der Information und Aufklärung der Forschungsteilnehmenden und der Transparenz der Humanforschung aufzeigen. Dass

^{iv} Für die Berichte aller genannten Ressortforschungsprojekte siehe: <https://www.bag.admin.ch/bag/de/home/das-bag/ressortforschung-evaluation/forschung-im-bag/forschung-biomedizin/ressortforschungsprojekte-humanforschung.html> [Stand 19.12.2019].

die wissenschaftliche Dimension in der vorliegenden Analyse kritischer diskutiert wird, widerspricht aber nicht den bisherigen Ergebnissen. Eher haben wahrscheinlich die externen Fachpersonen mit einem wissenschaftlichen Hintergrund und begrenzten Kenntnissen der schweizerischen Regelung stärker auf wissenschaftliche Aspekte fokussiert. Insgesamt gibt die vorliegende Analyse erste Einblicke in die Qualität der Forschungsaktivitäten im Rahmen des HFG und ergänzt damit die bisherigen Ansätze und Ergebnisse der Ressortforschungsprojekte und der Evaluation des HFG.

Résumé

Évaluation de la loi relative à la recherche sur l'être humain (LRH) en vigueur depuis 2014

La loi fédérale relative à la recherche sur l'être humain (LRH), assortie de ses ordonnances d'exécution, est en vigueur depuis 2014. En plus de son but primaire de protéger les êtres humains dans le cadre de la recherche, la loi vise également à assurer la qualité et la transparence de la recherche sur l'être humain et à aménager des conditions favorables pour des telles recherches. Dans la structure fédéraliste de la Suisse, les commissions cantonales d'éthique (CE) sont compétentes pour octroyer les autorisations pour des projets de recherche sur l'être humain (PRH). En fonction du type de projet, une autorisation délivrée par l'Institut suisse des produits thérapeutiques (Swissmedic) ou par l'Office fédéral de la santé publique (OFSP) peut aussi être exigée.

Afin d'examiner l'efficacité de la nouvelle LRH et d'identifier les potentiels d'optimisation, l'OFSP a chargé l'Institut de science politique de l'Université de Zurich (IPZ) et KEK-CDC Consultants d'évaluer la LRH. L'évaluation de la LRH s'appuie sur plusieurs méthodes et prend en compte les perspectives des différentes parties prenantes à la recherche sur l'être humain. L'évaluation avait également pour but d'analyser la qualité des activités de recherche soumises à autorisation en vertu de la LRH. En raison des contraintes temporelles et de la complexité de cette analyse, elle a dû être séparée de l'évaluation.

Analyse de la qualité d'une sélection de projets de recherche sur l'être humain (PRH) par des experts externes

L'analyse de la qualité des PRH exploratoire porte sur 13 projets sélectionnés qui ont été soumis aux CE en 2016. Elle a pour objectif d'obtenir des appréciations qualitatives des activités de recherche variées qui s'inscrivent dans le cadre de la LRH. C'est pourquoi la sélection des PRH analysés prend en considération l'entière des sept CE et les huit types d'études les plus fréquents. En conséquence, les PRH analysés sont soumis à l'ordonnance sur les essais cliniques (OClin) ou à l'ordonnance relative à la recherche sur l'être humain (ORH). Traitant de divers sujets, les PRH analysés ont surtout été initiés par les investigateurs, mais l'analyse couvre également des PRH initiés par l'industrie ou par des tiers. Il faut tenir compte du fait qu'en 2016, lorsque les PRH analysés ont été soumis, une partie des activités de mise en œuvre de la LRH n'étaient pas encore complètement établies et éprouvées.^v

Afin d'assurer une appréciation systématique, nous avons développé des critères de qualité de la recherche sur l'être humain en nous basant sur la réglementation suisse, les directives internationales, la littérature et une discussion avec le groupe d'accompagnement de l'évaluation de la LRH. Les critères de qualité de la recherche sur l'être humain comprennent huit critères au total qui sont attribués soit à une dimension scientifique, soit à une dimension éthique. Tous les critères doivent être pris en compte pour juger des risques, des contraintes et des bénéfices associés à un PRH.

Nous avons mandaté quatre experts externes résidant à l'étranger pour analyser la qualité des différents PRH sélectionnés en fonction des critères de qualité de la recherche sur l'être humain. Les analyses des experts externes sont basées sur les dossiers électroniques disponibles auprès des CE et, le cas échéant, de Swissmedic. Ces dossiers contiennent, entre autres documents, le protocole d'étude et les

^v Pour de plus amples informations sur les activités de mise en œuvre de la LRH, voir l'évaluation de la LRH:

Widmer, Thomas/ Frey, Kathrin/ Eberli, Daniela/ Schläpfer, Basil/ Rickenbacher, Julia (2019): Évaluation de la loi relative à la recherche sur l'être humain (LRH). Executive Summary. Zurich: Institut de science politique de l'Université de Zurich et KEK-CDC Consultants.

Widmer, Thomas/ Frey, Kathrin/ Eberli, Daniela/ Schläpfer, Basil/ Rickenbacher, Julia (2019): Evaluation des Humanforschungsgesetzes (HFG). Schlussbericht. Zürich: Institut für Politikwissenschaft der Universität Zürich und KEK-CDC Consultants.

informations destinées aux participants à la recherche, mais aussi les décisions des autorités. L'analyse se limite à la procédure jusqu'à l'autorisation initiale des PRH analysés. Compte tenu de la confidentialité des données analysées, les résultats ne sont présentés que sous la forme d'une synthèse globale des analyses individuelles des 13 PRH.

Bilan largement positif de la qualité des PRH, avec quelques réserves quant au design de recherche

Dans l'ensemble, l'analyse montre que les experts externes portent une appréciation largement positive sur la qualité des 13 PRH sélectionnés. Pour la plupart des PRH analysés, les spécialistes externes ont exprimé peu ou pas de réserve quant à un ou quelques critères de qualité. Le plus souvent, les experts externes manquent d'informations sur les analyses (planifiées) et se demandent si les PRH produiront des résultats fiables. Ils constatent également que les critères de sélection des participants à la recherche ne sont pas toujours documentés de manière exhaustive ou qu'ils sont trop strictement définis. Dans quelques cas, les experts externes manquent d'informations sur la répartition des tâches au sein du PRH. Les résultats tendent en outre à indiquer que la documentation contient essentiellement des précisions sur les publications scientifiques planifiées, alors que les informations sur la manière dont les participants à la recherche seront informés des résultats de l'étude ne sont pas disponibles. Les experts externes n'ont formulé des réserves sérieuses au sujet d'un PRH que dans des cas singuliers. Ces réserves sont principalement liées à des faiblesses considérables dans le design de recherche et, en partie au manque connexe d'expertise des investigateurs en recherche clinique.

Meilleure qualité des PRH initiés par l'industrie, aucune différence entre les types d'études

Étant donné que 13 PRH ont été analysés, nous ne pouvons que tirer des conclusions limitées sur les différences entre les PRH. En général, les experts externes donnent une appréciation nettement plus positive de la qualité des PRH initiés par l'industrie ou des PRH internationaux que de celle des PRH initiés par les investigateurs. Ce résultat est corroboré par des recherches sectorielles sur l'exhaustivité et l'exactitude des protocoles d'essais cliniques contrôlés randomisés soumis aux CE suisses en 2012 et 2016.^{vi} De plus, même si une autorisation était déjà exigée avant la LRH pour la plupart des études relevant du champ d'application de la ClinO, nous n'observons pas de différences systématiques entre les appréciations de la qualité des PRH soumis à la OClin et celles des PRH soumis à la ORH. Une différence notable réside en revanche dans le fait que les experts externes ne se sont préoccupés que de la pertinence de la question de recherche pour les PRH soumis à l'ORH.

L'analyse confirme en outre le jugement globalement positif des décisions des autorités et l'accent mis sur la protection et l'information des participants par les autorités. Les experts externes estiment que les décisions des CE et de Swissmedic sont largement compréhensibles et fondées. Conformément aux bases légales, les remarques de Swissmedic à propos des cinq PRH dans sa responsabilité ont porté essentiellement sur la qualité et la sécurité des produits thérapeutiques utilisés. Les commentaires des CE, qui ont dû autoriser les 13 PRH, sont souvent décrits par les experts externes comme appropriés ou très utiles. Toutefois, les experts externes soulignent également que certaines de leurs réserves ne sont pas reflétées dans les commentaires des CE. Celles-ci portent sur la pertinence du design de recherche, les critères de sélection des participants à la recherche et, dans un cas, la réutilisation de données ou d'échantillons sans le consentement préalable des personnes concernées.

^{vi} Les rapports sur tous les projets de recherche sectorielle mentionnés, voir : <https://www.bag.admin.ch/bag/fr/home/das-bag/resortforschung-evaluation/forschung-im-bag/forschung-biomedizin/ressortforschungsprojekte-humanforschung.html> [état au 1.4.2019].

L'accent mis sur des aspects scientifiques de la qualité complète les résultats existants

Les résultats de l'analyse de la qualité des PRH sélectionnés attirent par conséquent l'attention sur la dimension scientifique de la qualité de la recherche sur l'être humain et permettent ainsi d'élargir les résultats de l'évaluation de la LRH et de la recherche sectorielle. Les experts externes ont exprimé peu de réserves sur la qualité des PRH. Cependant, les réserves émises étaient relativement plus fréquentes sur les critères de la dimension scientifique que sur les critères de la dimension éthique. L'évaluation de la LRH et la recherche sectorielle soulignent quant à elles plutôt la dimension éthique car elles indiquent clairement la nécessité d'améliorer l'information des participants à la recherche et la transparence de la recherche sur l'être humain. Même si les résultats de l'analyse mettent l'accent sur la dimension scientifique, ils ne sont pas contradictoires aux résultats existants. Les experts externes, avec leur parcours académique et professionnel et des connaissances limitées de la réglementation suisse, ont probablement focalisé leurs appréciations sur des aspects scientifiques. En somme, la présente analyse offre un premier regard sur la qualité des activités de recherche soumises à la LRH et complète les approches et résultats de l'évaluation de la LRH et des projets de recherche sectorielle.

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Abbreviations

| | |
|------------|--|
| BASEC | Business Administration System for Ethics Committees |
| ClinO | Clinical Trials Ordinance |
| CRF | Case Report Form |
| CTU | Clinical Trial Unit |
| EC | Ethics committee |
| EU | European Union |
| FOEN | Federal Office for the Environment |
| FOPH | Federal Office of Public Health |
| GMO | pathogenic/genetically modified organisms |
| GT | Gene therapy |
| HRA | Human Research Act |
| HRO | Human Research Ordinance |
| HRP | Human research project |
| IPZ | Department of Political Science at the University Zurich |
| kofam | Coordination Office for Human Research |
| OrgO-HRA | HRA Organisation Ordinance |
| PI | Principal Investigator |
| SAE | serious adverse event |
| SCTO | Swiss Clinical Trial Organisation |
| SECB | Swiss Expert Committee for Biosafety |
| SNCTP | Swiss National Clinical Trials Portal |
| SNSF | Swiss National Science Foundation |
| SUSAR | Suspected unexpected serious adverse reaction |
| Swissmedic | Swiss Agency for Therapeutic Products |
| TpP | Transplant products |
| WHO | World Health Organization |

1 Introduction

1.1 Human Research Act (HRA): Swiss regulation of research involving humans

In Switzerland, research on diseases and on the structure and function of the human body is regulated in the Federal Act on Research involving Human Beings (Human Research Act, HRA; SR 810.30). As specified in Art. 1 of the HRA, its primary purpose is “to protect the dignity, privacy, and health of humans being involved in research”. Secondary purposes are to create favourable conditions for research involving humans and to contribute to ensuring the quality and transparency of such research. Detailed provisions for the implementation of the HRA are specified in the Ordinance on Clinical Trials in Human Research (ClinO; SR 810.305), the Ordinance on Human Research with the Exception of Clinical Trials (HRO; SR 810.301), and the Ordinance on Organisational Aspects of the Human Research Act (OrgO-HRA; SR 810.308).

The HRA and its associated ordinances have been in force since 1 January 2014 and brought several key innovations:

- Introduction of a nationwide regulation of research involving humans.
- Extension of the scope of research involving humans that requires authorization: In addition to clinical trials, which had mostly already been regulated, research with non-anonymized biological or gene material and research with health-related personal data also requires authorization.
- Introduction of the risk-adapted approach, which implies that the provisions for authorization and reporting differ depending on the risks and burdens associated with the research activities planned. The risk is indicated by three categories ranging from A (lowest) to C (highest).
- Clarification of the responsibilities of the authorities responsible for approving research involving humans, introduction of the lead procedure for ethics committees in the case of multicentre studies, determination of processing deadlines for the authorities.

The HRA is implemented at several levels in federal Switzerland. The cantonal ethics committees (ECs) are responsible for the approval of every human research project (HRP). While each canton needs to designate an EC, the cantons can also appoint a common EC. Currently, seven cantonal ECs exist. The ECs have founded a joint association called swissethics.

Depending on the type and risk of the HRP, an additional approval or a statement from a national authority is required. Clinical trials with medicinal products or medical devices entailing an elevated risk also require the approval of the Swiss Agency for Therapeutic Products (Swissmedic). Clinical trials of transplantation need also to be approved by the Federal Office of Public Health (FOPH).¹ The FOPH further manages the Coordination Office for Human Research (kofam) that aims at ensuring the exchange of the involved authorities and at informing the public about the Swiss regulation on research involving humans.

1.2 Evaluation of the HRA and analysis of the quality of selected human research projects (HRPs)

Based on the evaluation clause in Art. 61 of the HRA, the FOPH has commissioned the Department of Political Science at the University of Zurich (IPZ) and KEK-CDC Consultants to evaluate the HRA. The evaluation addresses the following four main questions:

- 1) How is the human research regulation being implemented?

¹ The Swiss Expert Committee for Biosafety (SECB), the Federal Office of Environment (FOEN) and the FOPH are further involved in authorization procedures by writing statements.

- 2) Is the HRA achieving the desired effects as stated in the article defining the purpose of the HRA (Art. 1)? Are there unintended effects (positive, negative, possible interactions)?
- 3) Which context factors influence the implementation of the HRA?
- 4) How can the human research regulation and its implementation be improved?

In order to take the different perspectives of the actors involved in the HRA into account, the evaluation used several methods and sources (see Table A 1 in the Appendix). On the one hand, we conducted interviews, surveys and workshops with the diverse stakeholders involved and we employed extensive document analyses and secondary data analyses. On the other hand, we relied on government research projects that were commissioned by the FOPH and aimed at investigating specific aspects of the HRA. Feedback of the evaluation's FOPH in-house steering group and an advisory group has been integrated continuously in evaluation conduct and reporting. The evaluation took place between August 2017 and June 2019. The final evaluation report was submitted in Mid-August 2019 (Widmer et al. 2019a)².

Next to other relevant aspects, the evaluation of the HRA also aimed at analysing the quality of research activities that are subject to the HRA. For this purpose, we commissioned external specialists to assess the quality of 13 selected HRPs on the basis of the application dossiers submitted to the authorities and the corresponding decision letters of the authorities. For their assessment, the external specialists relied on human research quality criteria that we developed. Because of the complexity of this endeavour and the diverse actors involved, it soon became apparent that it is not possible to conduct the analysis within the timeframe planned for the evaluation of the HRA.³ This is why the analysis of the quality of selected HRPs is presented in this separate report.

The objective of the present analysis is to provide qualitative information about the applications for authorization of HRPs and the decisions made by the authorities. It thus speaks to the evaluation questions on the implementation of the HRA and its effects, namely on how the HRA ensures the quality of research involving human beings as stated in its Art. 1 (questions no. 1 and 2). It is not the objective of the present analysis to compare the external specialists' assessments of the quality of the selected HRPs with the respective decisions of the authorities, namely the ECs. The ECs are responsible for assessing whether HRPs and the conduct thereof meet the ethical, legal and scientific requirements stipulated in the HRA. In particular, the ECs are responsible for assessing whether the protection of the persons concerned is guaranteed (Art. 51 HRA). Therefore, the ECs prioritize ethical to scientific considerations and aim at integrating multiple disciplines to comprehensively assess the risks and benefits of an HRP (swissethics 2013; Widmer et al. 2019a: 27). The external specialists, on the other hand, were commissioned to assess the extent to which the selected HRPs fulfil the human research quality criteria. Lastly, because Swissmedic is responsible for reviewing the safety and quality of the therapeutic product used, comparisons between Swissmedic's and the external specialists' assessments seem less evident.⁴

1.3 Outline of the report at hand

This report adds to the evaluation of the HRA and presents the analysis of the quality of selected HRPs. Following these introductory remarks, Chapter 2 outlines the methodical approach of the analysis. Chapter 3 explains the quality criteria used for the analysis. Chapter 4 presents and discusses the main results, which are based on a synthesis of the analyses of quality of the individual HRPs conducted by four external specialists. Chapter 5 summarizes purpose, background and main results of the analysis.

² The main report has been written in German. English and French translations of the executive summary are available.

³ Detailed information about the diverse steps needed to conduct the present analysis are outlined in Chapter 2.

⁴ Swissmedic's tasks are stipulated in Art. 32 ClinO and the Therapeutic Products Act (SR 812.21), incl. its ordinances.

2 Methods and approach

Several tasks were necessary to conduct the analysis of the quality of selected HRPs. First, we selected the HRPs to be analysed and gained permission to access the electronic documentation of the selected HRPs' application dossiers. In parallel, we developed human research quality criteria as a conceptual framework for the analysis. Afterwards, we commissioned external specialists to provide individual assessments of the quality of the selected HRPs. Lastly, we synthesized the results of the individual reports. The following sections describe these steps in detail and discuss limitations of our approach.

2.1 Case selection of the HRPs and description of the selected HRPs

After consultation with the FOPH, we initially selected 18 approved HRPs to be analysed.⁵ The selection aims at covering the diversity of study types of research involving humans requiring authorization according to the HRA and its associated ordinances. Therefore, two HRPs each were selected from the nine most frequent study types. Applications from all seven ECs were selected.⁶ For the respective EC, study types were selected with which it deals relatively frequently both in comparison with its number of other applications and in comparison with other ECs' number of applications. The objective of this approach is to select (fairly) typical cases of an EC. The single HRPs within one study type and EC have then been selected at random from all HRPs submitted to all the ECs in 2016 that eventually received approval. This allowed choosing HRPs that were, at the time, in the process of being conducted or had already been completed.

Due to amendments in the course of the work, the present analysis effectively covers 13 of the 18 initially selected HRPs.⁷ On the one hand, the researchers involved⁸ in three HRPs did not give their consent for the external specialists to access the application documentation. On the other hand, an external analysis of two HRPs was not feasible because of their language and topic. Table 1 illustrates the case selection by giving an overview of all applications approved in 2016 per study type and EC. One HRP was selected within every cell shaded in grey. The present analysis focuses on the HRPs in the cells shaded in dark grey. Table 1 thus shows that although the number of the analysed HRPs had to be reduced, the present analysis still covers all seven ECs and eight of the nine most frequent study types.

⁵ We first proposed to also select three HRPs that the authorities rejected. However, the ECs did not agree with this proposition. HRPs that have been rejected or withdrawn were later integrated in the evaluation by means of interviews with applicants of such HRPs.


⁶ At first, six ECs agreed to the analysis of the research quality of selected HRPs with the seventh EC only later agreeing to the analysis. As we had contacted researchers of the selected HRPs in the meantime, minor adaptations to the initial selection were needed.


⁷ As a part of the evaluation of the HRA, interviews with the applicants of all the 18 HRPs were conducted. The interviews aimed at assessing the applicant's perception of the authorization procedure concerning the specific HRP as well as generally, see Chapter 4 in the evaluation report (Widmer et al. 2019a: 39-49).

⁸ We use the term "researchers involved" as an umbrella term that comprehends principal investigators (ClinO), project leaders (HRO), sponsors, applicants or third parties involved.

Table 1: Number of applications submitted and approved in 2016 per EC and selected HRP

| | Applications submitted and approved in 2016 | | | | | | | |
|--|---|------------|---------------------------|------------|------------|------------|---------------------|-----------|
| | Total | Zurich | North Central Switzerland | Vaud | Bern | Geneva | Eastern Switzerland | Ticino |
| Clinical trials of medicinal products, transplant products (TpP), gene therapy (GT) or pathogenic/ genetically modified organisms (GMO) | 222 | 54 | 54 | 25 | 41 | 14 | 16 | 18 |
| Category A medicinal products | 24 | 3 | 4 | 4 | 7 | 2 | 4 | - |
| Category B medicinal products | 54 | 10 | 17 | 6 | 11 | 5 | 1 | 4 |
| Category C medicinal products | 141 | 40 | 33 | 14 | 23 | 6 | 11 | 14 |
| Category C TpP | 3 | 1 | - | 1 | - | 1 | - | 0 |
| Category C GT / GMO | 0 | - | - | - | 0 | - | - | - |
| Clinical trials of medical devices | | 45 | 21 | 8 | 22 | 11 | 7 | 4 |
| Category A | 88 | 32 | 16 | 6 | 15 | 9 | 6 | 4 |
| Category C | 30 | 13 | 5 | 2 | 7 | 2 | 1 | - |
| Other clinical trials | | 44 | 37 | 19 | 22 | 23 | 11 | 9 |
| Category A | 146 | 39 | 33 | 18 | 17 | 21 | 10 | 8 |
| Category B | 19 | 4 | 4 | 1 | 5 | 2 | 1 | 1 |
| HRP besides clinical trials | | 384 | 306 | 299 | 202 | 157 | 49 | 35 |
| Including persons, category A | 625 | 125 | 137 | 148 | 85 | 86 | 25 | 19 |
| Including persons, category B | 21 | 7 | 5 | 4 | 2 | 3 | - | - |
| Further use of health-related data and/or biological material | 766 | 248 | 158 | 145 | 114 | 62 | 24 | 16 |
| Including deceased | 18 | 4 | 7 | 2 | - | 5 | - | - |
| Including embryos & fetuses | 2 | - | - | - | 1 | 1 | - | - |
| Total | 1937 | 527 | 418 | 351 | 287 | 205 | 83 | 66 |

 1 application selected; analysis conducted

 1 application selected; analysis not feasible

Source: The data are excerpted from BASEC, received from swissethics on 30 October 2017.

- : no applications submitted / 0 : at least 1 application submitted, but no applications with a final decision of "approved".

Not included in the table because no applications existed within Switzerland in 2016: Clinical trials of TpP or GT/GMO in category A or B, clinical trials of transplantation.

Table 2 further presents main characteristics of the 13 HRP selected for the present analysis. It shows that about three quarters of the selected HRP was initiated by the investigator (9 out of 13), while about one quarter was initiated by the industry (3 out of 13). In line with this, the majority of the selected HRP was conducted in one site in Switzerland. 3 out of the 13 selected HRP are international, multi-centre studies, which implies that these HRP needed to be submitted to ethical review in other countries as well. As regards the authorization procedure, 5 out of the 13 selected HRP required approval by Swissmedic. The EC made their first decision about the selected HRP mainly under the regular procedure that requires participation of at least seven EC members and shall ensure expert and interdisciplinary assessment of the application for the conduct of an HRP (Art. 5 OrgO-HRA). In this first decision, the ECs most often did not approve the HRP but specified "conditions". The duration of the whole authorization procedure from first submission to final decision varies remarkably, the median lies at 90 days.

Table 2: Characteristics of the selected HRP and all approved HRP in 2016

| | | HRPs selected for the present analysis (N=13) | | All HRP approved in 2016 (N=1381) | |
|--|-----------------------------------|---|----------|-----------------------------------|----------|
| | | Number | Per cent | Number | Per cent |
| <i>Characteristics of the HRP</i> | | | | | |
| Ordinance | ClinO | 8 | 61.5% | 324 | 23.5% |
| | HRO | 5 | 38.5% | 1057 | 76.5% |
| Initiated by | Investigator | 9 | 69.2% | 1192 | 86.3% |
| | Industry | 3 | 23.1% | 189 | 13.7% |
| | Other | 1 | 7.7% | n. a. | n. a. |
| Number of sites | Monocentric | 9 | 69.2% | 1007 | 72.9% |
| | Multicentre Switzerland | 1 | 7.7% | 94 | 6.8% |
| | Multicentre international | 3 | 23.1% | 280 | 20.3% |
| Research to obtain degree | | 4 | 30.8% | 558 | 40.4% |
| <i>Characteristics of the process at the authorities</i> | | | | | |
| Authorities involved | EC | 8 | 61.5% | 1235 | 89.4% |
| | EC and Swissmedic | 5 | 38.5% | 146 | 10.6% |
| EC's first decision | Approved | 1 | 7.7% | 222 | 16.1% |
| | Approved, charges | 5 | 38.5% | 488 | 35.3% |
| | Not approved, conditions | 7 | 53.8% | 667 | 48.3% |
| | Declined or not considered | n. a. | n. a. | 4 | 0.2% |
| EC review procedure* (first decision) | Ordinary | 7 | 53.8% | 225 | 16.3% |
| | Simplified | 5 | 38.5% | 1033 | 74.8% |
| | Presidential | 0 | 0.0% | 123 | 8.9% |
| | Unknown | 1 | 7.7% | 0 | 0.0% |
| Duration from first submission to EC's final approval | Median | 90 | | 64 | |
| | Minimum | 20 | | n. a. | |
| | Maximum | 198 | | n. a. | |

Source for information on all HRP approved in 2016: Clinical Trial Unit Basel (2018a: 18, 20, 21, 24, 27, 58).

* Presidential review procedure was not possible in the selected cases. In relation to first decisions, the presidential review procedure may only be used in the case of applications that concern research involving the further use of biological material or health-related personal data with informed consent, see Art. 7 OrgO-HRA.

The selected HRP cover a wide range of topics in research involving human beings. Regarding the field of specialty, the selected HRP address questions in anaesthesiology, clinical pharmacology and toxicology, dental medicine, gynaecology and obstetrics, neurology, otorhinolaryngology, oral and maxillofacial surgery, paediatrics, psychiatry, and rheumatology.

As outlined above, the objective of the selection of the HRP was not to gain a representative sample of all HRP approved in 2016. Rather, the aim was to capture the diversity of research involving humans requiring authorization. In view of the considerable heterogeneity of the HRP, a larger number should have been analysed in detail in order to adequately reflect this diversity. Notwithstanding these limitations, Table 2 also provides the statistics of all approved HRP in 2016.⁹ It shows that while the selection approach led to an overemphasis of HRP regulated in the ClinO and an underemphasis of HRP in French-speaking Switzerland, the distribution of many main characteristics is fairly adequate. For example, the majority of the selected HRP is monocentric, investigator-initiated and received a first decision of "charges" or "conditions". Furthermore, HRP mainly conducted to obtain a degree are also represented in the present analysis. Based on these considerations, we conclude that our sample is not biased to such an extent that the findings could be called into question.

⁹ The statistics for 2016 only cover HRP that have been submitted and approved in 2016 because BASEC has only been used by all EC as of January 2016. HRP that have been submitted before 2016 may thus not be included. However, comparing the main statistics suggests that the relative numbers do not vary considerably between 2016 and 2017 (Clinical Trial Unit Basel 2018a, 2018b).

2.2 Bases: Application dossiers of the HRP and human research quality criteria

2.2.1 Documentary basis: electronic dossiers of the applications for authorization of the HRP

The electronic documentation of the HRP available at the ECs and, if applicable, Swissmedic is the main source for the analysis. Because many documents can be collected during the authorization procedure and the conduct of an HRP, the analysis focuses on the authorization procedure until first approval. Two versions of the application dossiers and the corresponding decision letters are of particular interest:

(1) Original submission:

Dossier of the application that has been submitted for the first time, including the decision letter of the authorities regarding this submission.

(2) First approved submission:¹⁰

Dossier of the application that has been approved without charges, including the decision letter of the authorities communicating the approval.

If the authorities approve the original submission, the two versions are identical. There may also exist additional versions of the application dossiers as well as correspondence between the authorities and the applicants.¹¹ Consequently, however, the present analysis does not cover documents submitted or decisions made during the conduct or at the end of the HRP. Eventual substantial amendments to an HRP that require authorization, e.g. when another trial location is added or the PI changes, are thus not object of the investigation. This also applies for reports of events¹², annual reports of clinical trials or final reports of the HRP.

While the specific requirements for the submissions depend on the type and properties of the HRP, the electronic documentation usually contains the following documents:¹³

- Cover letter
- Study protocol, incl. a synopsis of the HRP
- Patient, or more generally, participant information sheet and informed consent
- CV of the principal investigator (PI) or project leader
- Information on the nature and value of compensation for participants
- Information on secure handling and storage of biological material and personal data
- Decisions of the EC(s), if applicable Swissmedic

In order to enhance coordination, swissethics provides templates for several documents, namely for the study protocol, the participant information sheet and the ECs' decision letter (see Widmer et al. 2019a). In 2016, when the applicants submitted the selected HRP, templates were being revised or only being created (swissethics 2016, 2017). This is why we can observe different versions of templates in the application dossiers. In multilingual Switzerland, these documents exist in different languages. While the study plan and many other documents are often in English, participant information, correspondence with the authorities and the synopsis of the HRP are written in local language, i.e. German, French or Italian.

¹⁰ We use the term “first approved submission” because approval is also necessary in the later course of an HRP if there is a substantial amendment to the HRP.

¹¹ The PI respectively project leader or the sponsor may submit the application for authorization to the EC (Art. 24 ClinO; Art. 14 HRO). Applications for authorization by Swissmedic must be submitted by the sponsor (Art. 31 ClinO).

¹² I.e., serious adverse event (SAE) or suspected unexpected serious adverse reaction (SUSAR)

¹³ An overview of the documents to be submitted per study type is provided on swissethics' website: https://www.swissethics.ch/BASEC_assets/BASEC_ListOfAllDocuments.pdf [accessed: 11.10.2019].

Because the application dossiers contain very sensitive and confidential information, the authorities (EC, Swissmedic) and the researchers' permissions were needed to access the documentation. Following initial contact during spring 2018, we informed the responsible researchers in detail about the analysis at the end of 2018. On the basis of this detailed information we requested permission¹⁴ for us and the external specialists to access the application dossiers at the authorities. The present analysis covers only HRP in which the responsible researchers have explicitly consented to the analysis. The authorities were involved throughout this process of information and getting consent and made the electronic documentation of the selected HRP accessible to us.

2.2.2 Conceptual basis: Human Research Quality Criteria

A framework of human research quality criteria is used in order to have a meaningful reference for the assessment of the quality of the applications submitted and the decisions taken. We have developed these human research quality criteria in an iterative procedure. Generally, the criteria rest upon the legal bases (HRA and its ordinances, in particular the authorities' review areas), upon international guidelines and standards as well as upon relevant literature concerning quality of research on humans (Emanuel et al. 2000, 2008; Raspe et al. 2012; von Niederhäusern et al. 2017). A draft of the human research quality criteria was discussed with the advisory group of the evaluation of the HRA. Based on their feedback and then-newly published research (Gryaznov et al. 2018; von Niederhäusern et al. 2018), we have refined the criteria. The term "quality" and the human research quality criteria are presented and discussed in Chapter 3.

2.3 Procedure: Quality assessment by external specialists, synthesis by evaluation team

In order to obtain the expertise needed, we have commissioned external specialists to assess the quality of the selected HRP. We commissioned four external specialists to assess the quality of two to four HRP each.¹⁵ This proved feasible given the various topics of the selected HRP and the different languages of the application documents, but also given the time constraints of the internationally renowned external specialists. To avoid conflicts of interests and to strengthen the independence of the assessments as far as possible, only external specialists outside of Switzerland were contacted. All four external specialists who have eventually analysed the quality of the selected HRP are clearly established experts in their fields and possess considerable experience in reviewing research involving humans for the purpose of either systematic reviews or ethics committees. A list of the names and background information about the external specialists is provided in the Appendix 7.3. For confidentiality purposes, no information is provided on who analysed which HRP.

The external specialists gained access to the electronic documentation with the help of the University of Zurich's service to exchange confidential data. Like us, the external specialists are bound to confidentiality and are only allowed to access the electronic documentation of the selected HRP for the purpose of the analysis. They only had access to the electronic documentation of the HRP that they analysed.¹⁶

¹⁴ Consent was sought from the sponsor and the PI respectively project leader of the HRP. The number of permissions needed varied depending on the set-up of the HRP.

¹⁵ In total, seven external specialists were contacted.

¹⁶ The external specialists were only allowed to access the electronic documentation of the application until first approval. We were also allowed to access further information, either via BASEC or via Swissmedic. However, for the purpose of the present report, we only accessed information on BASEC to ensure that the application dossiers were complete. For the purpose of the evaluation, we also accessed BASEC to prepare the interviews with the applicants (see Widmer et al. 2019a: 39-49).

To support a systematic assessment and have a meaningful basis for the synthesis, we provided a template for the assessment of the individual HRP to the external specialists (see Appendix 7.2). The external specialists were specifically asked to explain and justify why they consider a quality criterion (not) fulfilled to a certain degree. Because the reports of the external specialists may allow identifying the individual selected HRPs, these reports are only for our attention. The external specialists reported their results in English or German.

For the synthesis, we conducted a qualitative content analysis of the specialists' assessments and, if necessary, descriptively analysed the application dossiers to better contextualize the results. On the one hand, we compiled and compared the specialists' assessments. In addition, we examined whether apparent differences exist between HRPs subject to ClinO versus HRO, between international and Swiss-focused HRPs and between investigator-initiated HRPs and industry trials. On the other hand, we read the application dossiers, in particular the synopses of the HRPs and the correspondence with the authorities. We also searched for entries of the HRPs in the Swiss National Clinical Trial Portal (SNTCP) and in the international registries of the World Health Organization (WHO) or the U.S. National Library of Medicine (clinicaltrials.gov).¹⁷ As a general rule, reporting of the results needs to be relatively abstract in order to prevent identifying any individual HRPs. Feedback of the external specialists on a draft version of the synthesis was integrated in the present report. In addition, we clarified a few issues with them when drafting the report.

2.4 Limitations: One qualitative analysis of 13 HRPs submitted two years after HRA enactment

While our methodological approach aims at providing qualitative statements on the broad area of research involving humans that is subject to the HRA, our methodological approach also comes with several limitations. Firstly, the number of HRPs analysed is small. We initially planned to analyse 18 approved HRPs, but eventually were able to conduct analyses of the quality of 13 approved HRPs. This means that we can, at best, draw tentative conclusions about differences in quality depending on the HRPs' characteristics, for example regarding study type. However, as explained above, primary goal of the analysis was not representativeness, but to cover the broad range of research involving humans subject to the HRA. Moreover, the present analysis was designed as to complement other analyses of the quality of research involving humans within the scope of the evaluation of the HRA and government research (Gryaznov et al. 2018; Widmer et al. 2019a).

Secondly, it needs to be taken into account that the HRPs analysed were approved in 2016 or early 2017 – two years after the HRA came into force. The evaluation has shown that there were initial difficulties in implementing the HRA because the necessary processes, structures and activities had not been fully in place when the HRA entered into force (Widmer et al. 2019a: 90). When the researchers submitted the HRPs analysed, there were many practical yet important changes, in particular regarding templates for study protocols or participant information (swissethics 2016, 2017, 2019a, 2019b). These developments may affect the quality of the HRPs selected and, eventually, the assessments thereof. Furthermore, the evaluation also showed learning processes at the end of the researchers and authorities after the enactment of the HRA. However, the present analysis cannot make any statements about the development of the HRPs' quality over time and the role of the HRA therein.

¹⁷ We searched for all HRPs in SNTCP by using their BASEC-No. If the entries in SNTCP were not linked to entries in international registries, we also searched on <http://apps.who.int/trialsearch/Default.aspx> and <https://www.clinicaltrials.gov> by using keywords from the HRP's title.

Thirdly, it needs to be noted that we can rely on one single assessment per HRP analysed by one of four external specialists. This seems necessary for feasibility purposes. While we have asked the external specialists to assess the human research quality based on a template, the external specialists still have different backgrounds and may have commented or not commented different elements of human research quality in their qualitative assessments. This needs to be considered when interpreting and discussing the results.

3 Conceptual framework: Human research quality criteria

The quality of research involving human beings is discussed in international guidelines and the Swiss legal basis: Helping “to ensure the quality of research involving human beings” is listed as one of the HRA’s secondary purposes (Art. 1, para. 2 HRA). However, “human research quality” as such is not defined in the legal bases. Several provisions describe the “scientific quality” (see Art. 5 or Art. 10 HRA). On the ordinance level, Art. 4 ClinO specifically relates to the “scientific quality”:

The sponsor and the investigator of a clinical trial shall ensure scientific quality. In particular:

- a. they shall define a research question based on the current state of scientific knowledge;*
- b. they shall use an appropriate scientific methodology; and*
- c. they shall ensure the availability of the resources required for the clinical trial and provide the necessary infrastructure.*

Art. 4 ClinO generally applies to research subject to the HRO as well.¹⁸ Next to these provisions related to the scientific quality, the term “quality” is also used in the legal provisions regarding the data quality and security (see Art. 5 ClinO) and the quality of the therapeutic product used (see, e.g., Art. 32 ClinO). Consequently, the elements of human research quality mentioned in the legal bases are part of the review areas of the authorities.¹⁹ More generally, this implies that the term “human research quality” does not solely entail scientific aspects (Rütsche 2015: 98).

The quality of research involving human beings is also examined in the literature concerning the value and ethical conduct of research involving humans. Von Niederhäusern et al. (2017) systematically searched conceptions of clinical research quality on websites of governmental bodies, regulatory agencies, the pharmaceutical industry, academic and commercial contract research organisations, initiatives, ethics committees, patient organisations and funding agencies. They find that clinical research quality is seldom explicitly defined and if, that different stakeholders emphasize different aspects of clinical research quality and different stages of research conduct. Therefore, von Niederhäusern et al. (2017) conclude that a consensus-based, broad conception of clinical research quality is desirable in order to increase the value of clinical research (see von Niederhäusern et al. 2018).²⁰ Such a broad conception of human research quality corresponds to the seven respectively eight principles of ethical clinical research according to Emanuel et al. (2000, 2008). As elaborated before, these principles are important foundations for the work of the Swiss ECs and beyond (Raspe et al. 2012; swissethics 2013).

The quality of the selected HRP was assessed on the basis of the human research quality criteria presented in Table 3. On the one hand, a total of *eight different quality criteria* are distinguished. The criteria are assigned either to *a scientific or an ethical dimension of research involving humans* for an easier handling and understanding. However, the two dimensions and different criteria rest inherently connected. On the other hand, the criteria can be assessed with respect to *four aspects of research involving humans*: (1) the conception and (2) the planned conduct of the HRP, (3) their presentation in the application and (4) the decision of the authorities.

¹⁸ More specifically, Art. 2 HRO postulates that Art. 4 ClinO applies *mutatis mutandis*.

¹⁹ In the HRO, “scientific quality” is specifically not mentioned as a review area for HRP involving further use.

²⁰ Based on their review of definitions of research quality and on online Delphi surveys, von Niederhäusern et al. (2018) have developed a framework for research quality called INQUIRE.

Table 3: Human research quality criteria

| | | | | Aspects | | | |
|----------------------|----|---|--|---|---|--|---|
| | | | | Concept | Conduct | Application | Decision |
| Scientific dimension | S1 | Relevance of the research question | <ul style="list-style-type: none"> • Scope of research (research question in the area of research involving humans; necessity of research involving humans to answer the research question) • Discussion of relevant previous research (with human- or non-human subjects) or exploratory analyses • Argumentation for relevance of the research question | Does the conception and preparation of the HRP ensure the fulfilment of the criteria? | Do the measures foreseen during the conduct of the HRP ensure the fulfilment of the criteria? | Does the application contain the information necessary to assess the criteria? Is the information provided clear and comprehensible? | Are the decisions of the authorities well-founded, comprehensible and fair? |
| | S2 | Suitability of the research design | <ul style="list-style-type: none"> • Suitability of the design to answer the research question (definition and measurement of variables, blinding, population size and relevance, timing of measurements and endpoint, treatment and assignment thereof, statistical method) • Pre-defined, standardized approach of collection, documentation and quality control of data (incl. anticipation of possible bias) | | | | |
| | S3 | Professional qualification | <ul style="list-style-type: none"> • Knowledge and experience of the principal investigator/project leader with regard to the subject investigated, project management and leadership | | | | |
| | S4 | Availability of resources and responsibilities | <ul style="list-style-type: none"> • Planning of necessary resources for the HRP with respect to finances, personnel, time, rooms, equipment, liability insurance, availability of potential participants • Clarification of responsibilities | | | | |
| Ethical dimension | E1 | Selection of the participants | <ul style="list-style-type: none"> • Suitability of inclusion and exclusion criteria to answer the research question • Fairness of selection (e.g. gender, children, other vulnerable groups, healthy volunteers versus patients) • Approach of recruiting participants, compensation of participants | Does the conception and preparation of the HRP ensure the fulfilment of the criteria? | Do the measures foreseen during the conduct of the HRP ensure the fulfilment of the criteria? | Does the application contain the information necessary to assess the criteria? Is the information provided clear and comprehensible? | Are the decisions of the authorities well-founded, comprehensible and fair? |
| | E2 | Information of the participants | <ul style="list-style-type: none"> • Design of the process of participant information and consent • Comprehensibility for laypersons in general and the group of participants in particular • Comprehensiveness (purpose of research and its procedures prior until after the project, potential risks, benefits and alternatives, rights and obligations, privacy policy) | | | | |
| | E3 | Protection and safety of the participants | <ul style="list-style-type: none"> • Provisions to minimize risks and burdens and to protect dignity, privacy and health of the participants: safety of products or devices used, dosage, radiation, protection and privacy measures for handling, access, analysis and storage of data and material (e.g. coding, only necessary information collected) | | | | |
| | E4 | Respect for and involvement of the participants | <ul style="list-style-type: none"> • Care during and after the project (handling of adverse or unexpected events, contact person, post-trial access to treatment) • Respect for participants (possibility of withdrawal, right to know and right not to know) • Availability of public information | | | | |

The main purpose of this framework of human research quality criteria is to assure a systematic assessment of the relevant aspects to the quality of HRPs. It is intended to be applicable to the different areas within research involving humans. Moreover, it is intended to reflect the diverse needs of the different stakeholders in research involving humans (researchers, participants, funding bodies and public, authorities) and to cover different phases of the research and authorization process. However, the framework with its eight criteria concerning four aspects shall not be understood as an additive index. Neither shall the order and abbreviations of the criteria indicate their relative importance. All criteria and aspects have an impact on the consideration of an HRP's risks and burdens relative to its benefit.²¹

²¹ This is also why we decided to not include the risk-benefit-ratio as an individual criterion.

4 Results

As outlined in Chapter 2.1, the external specialists have assessed the quality of total 13 HRP's belonging to eight different study types and covering diverse topics. While eight HRP's can be classified as clinical trials according to the Swiss regulation, five HRP's concern other research involving humans covered by the HRO. The majority of the HRP's analysed is focused on Switzerland, while three HRP's are part of international studies. About three quarters of the HRP's analysed were initiated by the investigator, the other quarter of the HRP's analysed was initiated by an industry company or a third party. Roughly half of the investigator-initiated HRP's received third party funding by the European Union (EU), the Swiss National Science Foundation (SNSF) or another institution. Moreover, about half of the investigator-initiated HRP's were principally conducted for obtaining a degree.

In what follows, the external specialists' assessments are synthesized and discussed. Firstly, the external specialists' individual assessments of the eight criteria are presented. Secondly, the external specialists' overall impression of the quality of the HRP's and the decisions made by the authorities is summarized. Lastly, the present results are discussed in the light of previous government research, the evaluation of the HRA and other literature.

4.1 Individual assessments of the human research quality criteria

4.1.1 Scientific dimension

The scientific dimension covers mainly questions about the research design and the resources needed to conduct this research. The assessment of this dimension is thus mostly based on the study plan and the CV or certificates of the PI or project leader, possibly also on additional information about the facilities where the HRP is being conducted.

Generally, we observe that the external specialists comment at length on the relevance of the research question (S1) and especially on the suitability of the research design (S2), while assessments of the professional qualification (S3) and of the availability of resources and responsibilities (S4) are shorter. Several reasons may explain this pattern. On the one hand, S1 and S2 can be conceived as broader in focus than S3 and S4. On the other hand, due to their academic background, the external specialists may emphasize S1 and S2. Furthermore, while S1 and S2 are mostly assessed on the basis of the detailed study plan, S3 and S4 can also be assessed on the basis of staff lists and CVs.

4.1.1.1 S1 – Relevance of the research question

Overall, the external specialists find the research question addressed in the HRP's analysed to be relevant and well justified in the light of previous research. In the majority of the 13 HRP's analysed, they observe that the research question is relevant as it addresses issues that are important with respect to the development of a medicinal product, to a certain disease or population or as it concerns an important public health issue. Moreover, the external specialists find that the research envisaged adds to previous research. In a few cases, however, the external specialists critically discuss whether answering the specific research question – while generally relevant – is justified in the light of the previous state of research presented in the study plan. In other, few cases, the external specialists question the relevance of the research question. While in one case, the research question is seen as too ambitious and unspecific, the external specialist wonders how the research question contributes to shedding light on a more general topic in another case.

With respect to the HRP's characteristics, we can observe that the relevance of the research question is critically discussed only for investigator-initiated HRP's covered by the HRO. More specifically, it concerns HRP's involving persons. One possible explanation for this pattern is that such research is more oriented towards understanding the functioning of the human body or diseases on a more general level. Yet, we can also notice that these investigator-initiated HRP's received funding from foundations. Therefore, the applicants already needed to convince peers of the relevance of their research in order to obtain a grant. On the contrary, the relevance of the research question is assessed more positively for the few international studies and, related to this, industry- or third-party-initiated HRP's and clinical trials.

4.1.1.2 S2 – Suitability of the research design

The external specialists find the research designs generally suitable in order to answer the research questions but often wish to have further information on the (planned) methodological procedures. In particular, they miss a detailed specification of outcomes of interest and how they are measured, of possible confounders and of the statistical tests used. The planned sample size is mostly estimated to be appropriate. The external specialists also specifically mention that monitoring or other measures to control data quality are in place with regard to four out of the eight clinical trials analysed.²² In a few cases, the external specialists observe that other methods can be expected to yield more solid results than the specific method chosen. This largely concerns the two retrospective HRP's based on further use of data or material. In a single case, the analysis reveals major concerns about the suitability of the research design. It is not only questioned whether the research design allows responding to the research question, but important information on the methodological procedure is missing and, if available, shows several shortcomings.

The external specialists take issue with the suitability of the research design for HRP's subject to the ClinO as well as to the HRO. As said, they question whether the retrospective analysis in the HRP's involving further use represents the most reliable methodological approach. This assessment may be partly affected by general attitudes about different research methods. However, regarding both HRP's involving further use, the external specialists also indicate that the description of the retrospective analysis does not provide sufficient information, e.g. regarding the specific variables used and their scales as well as the tests applied. Again, the assessment of S2 is very positive for HRP's that were initiated by the industry or third parties, while the external specialists only raise concerns in the case of investigator-initiated HRP's.

4.1.1.3 S3 – Professional qualification

For all the HRP's analysed, the external specialists have no or only minor concerns about the qualification of the PI or project leaders involved. In some applications, the external specialists could not deduce from the CV whether the project leader or the PI possesses all the necessary competencies needed to conduct the study, e.g. regarding statistical methods or one of the subfields of inquiry. Moreover, the external specialists also indicate that in order to properly assess S3, information is not only needed on the PI or the project leader but also on the personnel actually conducting the HRP (physicians, nurses,

²² It seems that not all external specialists paid equal attention to data management and monitoring. Moreover, the requirements regarding monitoring depend on the study type and the risks associated with the study. While adequate monitoring by the sponsor is required for clinical trials in accordance with GCP (see ClinO Art. 5 para 1; ClinO Annex 1), deviations from this requirement are possible depending on the risk and type of the trial (see ClinO Art. 5 para 3). For the HRP's subject to HRO, monitoring is only recommended but not required.

coordinators, statisticians) and consequently on the division of tasks.²³ Given the largely positive and rather brief assessment of S3, we cannot observe any considerable differences according to the HRP's characteristics.

4.1.1.4 S4 – Availability of resources and responsibilities

According to the assessments, the available resources and the responsibilities of the parties involved in the HRP are well documented in the application. Only in a few cases, the external specialists find that financial or time resources allocated to the HRP have not been sufficiently clarified. Connected to the explanations regarding the professional qualification above, the external specialists also sporadically miss information about who is responsible for what (see 4.1.1.3). With regard to HRP initiated by the industry, the external specialists state that responsibilities are in line with standard current practices.

The assessments of this criterion do not vary considerably in general and consequently also between HRP. Still, we can observe that the external specialists indicate a lack of information in the case of investigator-initiated HRP within the area of the HRO.

4.1.2 Ethical dimension

The ethical dimension draws the attention to those participating in the HRP. It covers questions about the suitability and fairness of selection as well as the process of recruiting and informing possible participants. The provisions to protect the participants and minimize their risks as well as care during and after the HRP is also assessed. Consequently, relevant documents are the study plan but also patient or participant information sheets and declarations of consent.

Similar to the scientific dimension, we can observe that the assessments of the selection (E1) and information of participants (E2) are more detailed than the assessments of the protection and safety of the participants (E3) as well as the respect for and involvement of them (E4). Because participant information needs to be written in the local language, it is not always available in the native language of the respective external specialist. While the external specialists indicate that they are able to generally evaluate the participant information, their ability to specifically assess whether the participant information is comprehensive for laypersons is possibly limited.

4.1.2.1 E1 – Selection of the participants

In the majority of the HRP analysed, the external specialists find the criteria for selecting the participants to be appropriate and suitable to answer the research question at hand. In about half of the HRP analysed, the external specialists indicate that selection criteria are clearly and adequately defined so that selection is fair, research involving vulnerable groups is – if applicable – well justified, and provisions to minimize selection bias are in place. In other cases, the external specialists either question the generalizability of the HRP's findings due to strict selection criteria or they miss detailed information about the selection criteria. More specifically, information is lacking on how exactly the participants are selected and contacted. In one case, the application does not contain explanations on how one of the main outcomes of interest can be measured given the participants selected. Only in single cases, we interpret the external specialists' concerns to be considerable. In these cases, the selection criteria seem

²³ For all study types the following information is to be submitted to the EC: the PI or the project leader's CV, including evidence of his or her knowledge and experience, and a list of the other persons involved in the research project, indicating their responsibilities and relevant professional knowledge (see HRO Annex 2, ClinO Annex 3). Our own reading shows that some information on the above-mentioned points was provided in the HRP analysed. Therefore, the external specialists' assessments suggest that this information was too vague.

to be too strictly defined. This not only implies that generalizability from these HRP is limited but also that selection is unfair. For example, in one case, women are excluded but the reason for this is not explained in the study plan.

The rationale of selecting participants and its description seem not to differ between the types of study but between the scope of the HRP. We observe that the study plans of the international HRP all contain comprehensive and clear information about the selection of participants. On the contrary, the external specialists identify major concerns regarding the selection process in two national HRP, one in the area of the HRO, the other in the area of the ClinO. However, we can also observe that there seems to be a trade-off between comprehensive selection of participants – implying higher generalizability – and feasibility of the HRP, as HRP with students as participants illustrate.

4.1.2.2 E2 – Information of the participants

Overall, the external specialists find the information issued to the participants adequate and the process of seeking informed consent well described. The external specialists also appreciate that information leaflets for different groups of participants and their families are provided. In a few cases, the external specialists question whether some of the terms used in the participant information is comprehensible to laypersons. As mentioned above, we can assume that it was not possible to assess thoroughly the language of the participant information for all external specialists. In one case, the external specialist wishes that contact information of the sponsor and not only of the PI were available on the participant information sheet. According to the Swiss regulations, the participant must receive information about the sponsor and main sources of funding for the HRP (see Art. 7 let. h ClinO, Art. 8 let. g HRO). In line with this requirement, the current swissethics template for participant information also contains remarks on the sponsor and funding of the HRP, but it requires only to indicate the contact details of the PI, and possibly his or her collaborators, to ensure care during the HRP.²⁴

Generally, the external specialists varied barely in their assessment of this criterion and we cannot observe any differences between the study types; however, a special case with respect to this criterion is human research involving further use. Informed consent was not sought in both HRP involving further use analysed, but it was instead issued by the ECs on the authority of Art. 34 HRA.²⁵ In one case, the external specialist challenges whether gathering informed consent is not feasible after all. The respective applicant argues that consent cannot be sought because many patients do not speak the local language, which would lead to a biased sample. However, the external specialist wonders whether informing the patients adequately would not be possible if treating them is. In the other case, the external specialist does not question why the applicant asks to resort to Art. 34 HRA.

4.1.2.3 E3 – Protection and safety of the participants

The external specialists assess the quality regarding the protection and safety of the participants largely positive. In the majority of the HRP analysed, they comment that the handling of data is specified and appropriate. In one instance, though, the external specialist questions whether the “clinical guidelines

²⁴ Previous versions of the swissethics template were in place when the applications for the analysed HRP were written. The participant information template is generally used by all researchers, while the templates for study protocols are mostly intended for investigator-initiated HRP. The current versions of the swissethics template in German, French and Italian are available on the swissethics' website. For clinical trials see: https://www.swissethics.ch/doc/ab2014/Template_Studieninformation_d.pdf [accessed: 21.10.2019].

²⁵ Art. 34 HRA stipulates that “[i]f the requirements for informed consent specified in Articles 32 and 33 are not met, further use may be made of biological material or health-related personal data for research purposes in exceptional cases if: a. it is impossible or disproportionately difficult to obtain consent or to provide information on the right to dissent, or this would impose an undue burden on the person concerned; b. no documented refusal is available; and c. the interests of research outweigh the interests of the person concerned in deciding on the further use of his or her biological material and data.”

for handling patient data”, to which the applicant refers, provide information in sufficient detail to warrant comprehensive protection of the data. The external specialists further state that the potential risks are detected, discussed and provisions to minimize the risks and to protect the participants are in place. For several HRP, the external specialists relativize also that the HRP only involves minimal to barely any risks to its participants. Given that we cannot observe much variation in the assessments of this criterion, there are also no differences between the different characteristics of the HRP.

4.1.2.4 E4 – Respect for and involvement of the participants

The external specialists generally raise few criticisms regarding the respect for and involvement of the participants. In their assessments of criterion E4, the external specialists most often discuss the availability of public information about the HRP, namely publication strategy. From these assessments, we can conclude that the study plans rather include information about publications targeted at peers than information about the HRP’s results to the attention of the participants. In three cases, the external specialists remark that there was no information on publication. However, in two cases, the external specialists do not deem this relevant because the respective HRP are either exploratory studies about a medicinal product or quality assurance studies on a medical device. As another element of public information, the external specialists sporadically refer to public registration. According to Art. 64 ClinO, HRP are required to be registered in the federal database (SNCTP) and in a primary registry recognized by the WHO or on clinicaltrials.gov. In two cases, the external specialists note that they did not find the HRP on clinicaltrials.gov. Since one of these two HRP is listed in the registry of the WHO, it still fulfils the legal provisions. Our own analyses show that all eight analysed HRP subject to ClinO are registered in the SNCTP. However, we could not find two out of the eight HRP in one of the applying international registries. As another aspect of E4, the external specialists further discuss care during and after the project. In one case, the external specialists did not find any information on this. Lastly, the external specialists highlight in several cases that it is possible for the participants to withdraw at any moment of the HRP.²⁶ Besides the differences between the HRP that are due to the regulations ClinO and HRO, we did not observe any differences between the HRP’s characteristics.

4.2 Overall assessment of the single HRP and the authorities’ comments

4.2.1 Overall impression of the quality of the single HRP and their applications

Next to the assessment of individual dimensions, we asked the external specialists to share their overall impression. The synthesis of these statements shows that the external specialists mostly have no or only minor concerns with respect to the HRP as a whole. These concerns mainly pertain to one or several criteria in the *scientific* dimension. More specifically, the external specialists miss information about the (planned) analyses, and they question whether the analyses will yield reliable results. Regarding the ethical dimension, the external specialists reiterate in their overall assessments concerns or questions about the selection of the participants. Selection criteria are not always comprehensively documented or are too strict in the opinion of the external specialists.

Only in single cases, the external specialists issue considerable concerns, as we understand it, about the overall HRP. In one case, the assessment shows that while the HRP’s general topic is of interest and appropriate measures to inform and protect the participants are in place, the research question is not sufficiently specified, and the methodological framework does not allow giving reliable answers. In

²⁶ In line with Art. 7 para. 2 HRA, our analysis shows that the participant information sheets of all HRP analysed include the right to revoke consent at any time without explaining the reasons for this.

another case, the external specialist concludes that the information in the application reveals several methodological shortcomings in clinical research and that sufficient quality can possibly only be obtained with considerable help of the authorities and subsequent external monitoring.

It goes without saying that the assessment of the external specialists clearly depends on whether the information provided in the application is clear and comprehensive. Based on the external specialists' comments about the individual dimensions, we can observe that the application documentation of the first approved submission is mostly complete and informative. As indicated above, though, the external specialists also remark that information is missing. This concerns several aspects of the research design and the rationale for selecting the participants. However, it also concerns the qualifications of the PI or project leader illustrated in the CV and the overall distribution of the research work.

4.2.2 Authorities' decisions

The authorities explain the results of their assessment of the application in decision letters, which consequently provide the most important information source for the present analysis, although other correspondence between the applicant and the authorities was also available. As stipulated in Table 2, the original submissions of the HRPs selected were most often not approved right away but the EC decided to set "conditions" for approval for 7 out of 13 HRPs. In 5 out of 13 HRPs, the ECs approved the original submission, but listed charges to be fulfilled within 30 days. Only in one case, the EC approved the original submission right away with no charges. Swissmedic's process is different than the authorization procedure at the ECs. Swissmedic usually does not ask to resubmit revised full applications but rather to append additional information or clarification to the original applications. In all five HRPs selected, Swissmedic enquired the sponsor to provide further respectively up-to-date information or to correct details indicated in its clinical trial application form.

Based on our reading of the decision letters, the explanations of the authorities mainly refer to the suitability of the research design, the selection, the information and the protection and safety of participants:

- Regarding the suitability of the research design (S2), the ECs asked in several cases to provide further information about the methodological procedure. In addition, the ECs and Swissmedic occasionally requested to improve the Case Report Form (CRF).
- The comments of the ECs regarding the selection of participants (E1) mostly concern the selection criteria, while the ECs had concerns about the compensation of participants or the approach of recruiting them only in single cases. The comments further indicate that in several cases, selection criteria were not clear to the EC because of contradictory information in the application. Only in a few cases, the ECs questioned the rationale for excluding or including certain groups of participants.
- The information of the participants (E2) was most often commented by the ECs. The comments often concern the comprehensibility of the participant information sheet, in a few cases the ECs requested to ensure time for reflection or the participant's ability to consent on a voluntary basis.
- In most of the HRPs selected, the ECs and Swissmedic also commented on the protection and safety of the participants (E3). In line with their review areas, the ECs' requests rather focused on handling and protecting data, such as using only identifiable information when necessary, while the Swissmedic's requests rather focused on the manufacturing and safety of the products respectively devices used.

In contrast, the authorities had no requests about the other criteria in the majority of the HRPs selected. Therefore, we can observe that the authorities' reservations rather concentrate on the ethical dimension of the human research quality criteria.

The external specialists have not assessed the authorities' decisions with respect to the individual human research quality criteria but rather provided an account of their overall impression. While these accounts seem to be influenced by the external specialist's individual perspective, all external specialists generally find the comments of the ECs and Swissmedic²⁷ comprehensible and well founded. In more than half of the HRP analysed, the external specialists have assessed the decisions only positively. One external specialist specifically highlights the efficiency of the ECs' work. Several external specialists describe the comments of the ECs to "make very much sense", to be "estimable", "very helpful" or "targeted at concrete problems". In one case, the external specialist also clearly states that Swissmedic and the EC have contributed to improving the quality of the HRP analysed and to helping applicants with limited expertise in clinical research.

Regarding the other HRPs analysed, the external specialists have raised criticism on different aspects:

- Several external specialists point to problems that they have identified in their assessment but that were not covered in the ECs' comments.²⁸ Consequently, they wonder whether the authorities could have considered these points as well. This concerns remarks on the selection criteria, the research design and the missing informed consent in an HRP involving further use. In this respect, one external specialist emphasizes that the ECs' comments are only focused at details but not at pitfalls of the research design that could impede the usefulness of the HRP. In another case, concerning one HRP involving further use, the external specialist wonders whether the EC could not have insisted on a more thorough explanation why it is not feasible to ask participants for their consent.
- One external specialist also considers the ECs' decision procedure and pointed to inconsistencies in this respect. In particular, this external specialist questions why a multicentre HRP is being approved with charges in two centres and not approved in another centre. The external specialist finds the charges mentioned in the decision letter to be more fundamental – and also difficult to take care of in 30 days' time given the international scale of the HRP at hand – than the conditions, which the external specialist considers to be formalities.²⁹ Generally, the external specialist notes that the members of the EC involved in the decision are not well balanced with regard to gender.

4.3 Discussion of the results in light of previous studies about the HRA

How can these results be interpreted in light of the evaluation of the HRA and other research about the HRA? Several findings presented above are consistent with the observations made in previous studies on the HRA:

Firstly, the synthesis confirms prior results indicating that *protocols of industry-initiated trials are of higher quality than protocols of investigator-initiated trials*. The synthesis shows that the quality assessments differ between industry-initiated or international HRPs and investigator-initiated HRPs. In particular, the external specialists have assessed the criteria of the relevance of the research question (S1), the suitability of the research design (S2), the availability of the resources and responsibilities (S4) and also the selection of participants (E1) more positively for the industry-initiated or international HRPs, while

²⁷ Because Swissmedic was involved in the authorization procedures of 5 out of the 13 HRPs, only few comments are available.

²⁸ As can be inferred from the explanations above, the external specialists did not always mention concerns that they but not the authorities have addressed. In other cases, they found the authorities' decisions fully appropriate despite their concerns.

²⁹ In fact, the charges concern amendments requested to the participant information sheet and clarifications requested regarding the study protocol, while the conditions concern a missing GCP certificate of the local PI and the definitive version of the contract. While the external specialists find the latter points to consist only of formalities, it can also be questioned why the missing GCP has not been remarked during formal check.

they miss information or have issued concerns about some of the investigator-initiated HRP³⁰. This supports the findings of Gryaznov et al. (2018) who analysed total 400 RCT study protocols submitted to the Swiss ECs in 2012 and 2016. Gryaznov et al. (2018: 6, 16) find that human research quality in terms of adherence to SPIRIT³¹ criteria improved significantly for investigator-initiated trials between 2012 and 2016. In contrast, adherence to SPIRIT items of industry-initiated RCT study protocols was already at a high level in 2012 and did not change significantly in 2016. This improvement of the quality of investigator-initiated RCT study protocols is not Swiss-specific, though. Gryaznov et al. (2018: 20) observe a similar pattern for RCT study protocols submitted to ECs in Germany and Canada. Since the improvement of the quality of investigator-initiated RCT was more pronounced in Switzerland, Gryaznov et al. (2018: 24) conclude that the HRA and its implementation activities, namely the templates for study protocols, may have contributed to this.

Secondly, the synthesis supports the *overall positive evaluation of the authorities' work*. The external specialists find the comments of the authorities to be well founded and comprehensible. This matches the impressions of the interviewed researchers in the evaluation of the HRA: They find the decisions of the ECs and Swissmedic largely comprehensible and well structured (Widmer 2019a: 44, see also von Elm and Briel 2019: 25). However, in line with one external specialist, some of the interviewed researchers also indicate that the ECs' comments focus too strongly on details that are not relevant for ethical review (Widmer 2019a: 44-45).

With respect to the ECs' work, thirdly, our own reading of the decision letters of the HRP³²s analysed confirm that the *ECs pay particular attention to the participant information* and thus criterion E2. In the evaluation of the HRA, the interviewed members of the ECs also indicated that examining the comprehensibility of the participant information is key in the authorization procedure (Widmer et al. 2019a: 28). Furthermore, the EC members interviewed by De Nardi et al. (2018: 6-8) state that they have the impression that researchers do not carefully draft participant information sheets. The evaluation of the HRA and government research suggest that researchers also observe that the ECs examine participant information very diligently, but the researchers find this helpful (Widmer 2019a: 47; see also von Elm and Briel 2019: 26-28).

Fourthly, related to participant information, the present synthesis also supports the *evaluation of the HRA's recommendations to increase transparency of research involving human beings*. The assessments of criterion E4 on the respect for and involvement of the participants shows that most of the HRP³³s analysed comply with the regulations on public registration. However, the external specialists' assessments also suggest that the explanations on publication strategy in the study protocols focus on planned publications for the scientific community rather than for the participants. In the evaluation of the HRA, the interviewed authorities state that the transparency about the results of HRP³⁴s needs to be improved (Widmer et al. 2019a: 37). This view is reinforced by the results of the surveys among organisations representing research participants and among research organisations (Widmer et al. 2019a: 76). Based on a survey among Swiss residents, Ehrler and Lebert (2018: 53) likewise state that the Swiss

³⁰ Two reasons may partly explain the differences between investigator-initiated and industry-initiated HRP³⁵s: Firstly, the investigator-initiated HRP³⁶s represent not only on applied research but also rather basic research: As outlined in 4.1.1.1, the external specialists had concerns about the relevance of the research question (S1) in the case of investigator-initiated HRP³⁷s that aim at understanding the functioning of the human body or diseases on a more general level. Yet, other investigator-initiated HRP³⁸s investigating the effect of medical devices or other interventions can be considered as applied research. Secondly, investigator-initiated HRP³⁹s may be of lower quality because they include HRP⁴⁰s by early career researchers seeking to obtain a degree. Four out of the nine investigator-initiated HRP⁴¹s were conducted primarily to obtain a degree but we cannot observe clear systematic differences, which may also be due to the small number of HRP⁴²s.

³¹ SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT), initiative launched in 2007. The SPIRIT statement including the criteria was published in 2013 after systematic review and consultation of experts (Gryaznov et al. 2018: 8).

public wishes to have more information about research involving humans and does not know the information currently offered.

At the same time, some findings of the present report also add complementary insights to the evaluation of the HRA and government research:

In particular, the present report draws our attention to *the scientific dimension of human research quality*. The external specialists relatively more often issue concerns about criteria related to the scientific dimension than about criteria related to the ethical dimension of human research quality. In single cases, the external specialists thus fear that the selected HRPs may produce what is termed in the literature as “waste”³² because the research question is not sufficiently specified, or the research design has flaws. The evaluation of the HRA also points to need for improvement of the HRA with respect to ensuring the quality of research involving human beings³³. However, the external specialists’ more critical view of the scientific dimension is somewhat contrary to previous results focusing on the researchers’ perspective (Widmer et al. 2019a: 45, von Elm and Briel 2018: 29-31): In surveys and interviews, the researchers questioned whether the ECs possess the relevant expertise to review the HRPs’ relevance and research design. The assessments of the external specialists thus imply that the ECs’ concerns regarding scientific questions may be well founded.

There are several reasons why the present report is rather focused on aspects of the scientific than the ethical dimension, while the evaluation of the HRA and government research point to the need to improve aspects in the latter dimension, such as participant information and research transparency. One explanation may be that the external specialists, due to their background as statisticians or physicians, perceived their role in the assessment as scientists and therefore concentrated on the scientific dimension. Other explanations may be practical: Ethical considerations regarding the protection and information of participants may be more difficult to assess without profound knowledge of the legal bases in Switzerland. Moreover, participant information was not always available in the native language of the external specialist. Another explanation emphasizes the role of the ECs: They have commented on the participant information in most cases and thus possibly have contributed to the overall quality of these documents that are important for the ethical dimension.

Lastly, the present analysis shows that the quality of the 13 selected HRPs approved in 2016 and early 2017 is largely positively assessed but it is *not possible to clearly specify to what extent the HRA contributes to ensuring and improving the quality of research involving human beings*. The evaluation of the HRA and government research can neither give an unequivocal answer to this question. The authorities and the researchers interviewed find that the quality of the applications has improved since the enactment of the HRA. Researchers prepare their submissions and their projects more carefully and are also more sensitive towards data protection issues (Frey et al. 2018; Gryaznov et al. 2018; Widmer et al. 2019a). However, the authorities interviewed also question the role of the HRA in increasing the quality of HRPs. Instead, they mention other important developments targeted at investigator-initiated HRPs, such as establishing the Swiss Clinical Trial Organisation (SCTO) and Clinical Trial Units (CTU) or activities to train researchers (Widmer et al. 2019a: 37). Moreover, the research organisations’ representatives surveyed within the evaluation of the HRA indicate that human research quality has not changed as a consequence of introducing the HRA (Widmer et al. 2019a: 74).

³² See, e.g., the series in *Lancet* 383(9912) about “Research: increasing value, reducing waste”, <https://www.thelancet.com/series/research> [accessed: 10.11.2019].

³³ In the surveys among research participant organisations and research organisations, the respondents indicate that there is potential to improve the HRA with respect to ensuring the quality of human research, however, they fail to clearly identify what needs to be improved (Widmer et al. 2019a: 76-79).

5 Conclusion

Overall, the present analysis shows that the external specialists assess the quality of the 13 selected HRPs largely positive. Regarding most of the analysed HRPs, the external specialists have no or only minor concerns with respect to one or few criteria. These concerns mostly focus on the relevance of the research question, the suitability of the research design and the criteria to select participants. More specifically, the external specialists miss information about the (planned) analyses, and they question whether the analyses will yield reliable results. They find that selection criteria are not always comprehensively documented or that they are too strictly defined. However, the assessments of the individual criteria also suggest that, in a few cases, the external specialists miss information about the division of tasks within the HRP and in particular about additional staff who supposedly carries out considerable parts of the work. Regarding the transparency of research and the involvement of the participants, the assessments are diverse and the results less clear, but they seem to indicate that the applications often contain information about the publication strategy to the attention of peers but not of participants. Only in single cases, the external specialists have considerable concerns about an HRP. These concerns mostly relate to major shortcomings in the research design, and partly connected to this, the principal investigators' limited expertise in clinical research.

Given that 13 HRPs were analysed, we can only make tentative inferences about differences between the HRPs. Most likely, we observe that the external specialists assessed the quality of industry-initiated or international HRPs more positively than the quality of investigator-initiated HRPs. In submissions of the former type, statistical methods, data management, in- and exclusion criteria are discussed in-depth. This gap between industry- and investigator-initiated HRPs is supported by previous government research, in which the completeness and accuracy of RCT study protocols submitted to the seven Swiss ECs in 2012 and 2016 was assessed (Gryaznov et al. 2018). This study shows that while the quality of study protocols of industry-initiated RCTs remained stable on a high level, the quality of study protocols of investigator-initiated RCTs significantly improved from 2012 to 2016. However, much of this effect seems to be due to an international commitment to enhancing the quality of investigator-initiated RCT study protocols than due to the changes in the Swiss regulations (Gryaznov et al. 2018: 20, 24).

We can observe a few, but no systematic differences for the selected HRPs subject to the HRO and the HRPs subject to the ClinO. One notable difference is that the external specialists only had concerns about the relevance of the research question for HRPs subject to the HRO. Another difference, which is connected to epistemological considerations, concerns the further use of already collected personal health-related data or biological material. In their assessments, the external specialists principally question whether these retrospective analyses represent the most solid design for establishing inferences. Taken together, our results suggest that even though most of the HRPs subject to ClinO required already approval prior to the HRA, there are no considerable differences between the assessments of the quality for studies subject to HRO compared to studies subject to ClinO.

The present synthesis further confirms the overall positive assessment of the authorities' decisions and their emphasis on matters related to the protection and information of participants. The external specialists find the authorities' decisions largely to be comprehensible and well founded. In some cases, they also highlight that the authorities have contributed to a learning process of the applicants. Because the review areas differ and because only 5 out of the 13 HRP analysed needed approval from Swiss-med, the assessments of the authorities' comments largely focus on the EC. While the external specialists often describe namely the ECs' comments as fully appropriate, very helpful or their procedures to be efficient, they also raise criticism in some instances. This mostly relates to concerns that the external specialists have but which they do not find reflected in the ECs' comments. More specifically, these

concerns pertain to the suitability of the research design, to the selection criteria and, in one case, to renouncing from gathering informed consent. In addition to these assessments of the external specialists, the analysis of the decision letters shows that the authorities focus in many of their comments on the protection of the participants, namely on the comprehensibility of the participant information (ECs) and the quality and safety of the product(s) used (Swissmedic).

The present study thus largely supports results of the evaluation of the HRA and government research, but also provides complementary insights into the scientific dimension of human research quality. The external specialists expressed still few, but relatively many concerns about criteria of the scientific dimension, in particular regarding the relevance of the research question and the suitability of the research design. Concerning the ethical dimension, the external specialists observed pitfalls in selecting the participants. Participant information, which clearly needs to be improved according to the evaluation of the HRA and government research on the comprehensibility of participant information, was assessed largely positively (De Nardi et al. 2019; Widmer et al. 2019a). One explanation for this emphasis on the scientific dimension is that the external specialists with an academic background may have focused more on scientific aspects. Another explanation may be that the ECs' comments have contributed to the perceived high quality of the participant information. Moreover, as De Nardi et al. (2018, 2019) argue, it can be assumed that the external specialists, similar to other persons who are regularly confronted and therefore familiar with medical jargon, cannot evaluate participant information from a layperson's perspective.

To conclude, this report presents the synthesis of four external specialists' qualitative assessments of 13 selected HRPs, which comes with several limitations. Not only but also for feasibility purposes, the analysis is limited to 13 HRPs. This means that it does not cover a large, representative sample of HRPs approved in Switzerland and that it allows drawing only tentative conclusions about differences between the characteristics of HRPs. Given the analysis' focus on HRPs submitted in 2016, no inferences about the improvement of the quality over time can be made. Moreover, the analysis is based on one assessment per HRP by an external specialist from outside of Switzerland. The external specialists' task was to assess the quality of the selected HRPs in a qualitative manner by relying on the human research quality criteria. This task differs from authorizing HRPs or from analysing the accuracy and completeness of HRPs (Gryaznov et al. 2018). The present analysis thus reveals exploratory findings about the quality of research activities within the HRA and complements approaches and findings of the evaluation of the HRA and government research projects.

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7 Appendix

7.1 Evaluation of the HRA: Structure, methods employed, and sources used

Table A 1: Summary of the methods used for the purpose of the evaluation of the HRA

| Module: Subject | Survey instruments/data sources |
|--|--|
| 1. Detailed concept and impact model | <ul style="list-style-type: none"> – 3 informational talks with HR stakeholders – Document analysis |
| 2. Brief description “Stakeholders and processes in HR” | <ul style="list-style-type: none"> – 8 interviews with HR stakeholders – Document analysis |
| 3. HRA implementation from the perspective of authorities and other stakeholders | <ul style="list-style-type: none"> – 14 interviews with ECs and federal agencies – Synthesis of government research; document analysis |
| 4. Implementation of the HRA from the perspective of researchers | <ul style="list-style-type: none"> – 31 telephone interviews with applicants (18 regarding authorised applications; 13 regarding rejected/withdrawn applications) – Synthesis of government research |
| 5. Analysis of research applications | <ul style="list-style-type: none"> – Secondary data analysis (including government research) – <i>separated</i>: Analysis of the quality of selected research applications³⁴ |
| 6. Effects “Protection/ rights of trial participants” | <ul style="list-style-type: none"> – Standardised online survey of organisations in the area of protection/ rights of trial participants (N=65 respondents from 51 organisations) – Synthesis of government research |
| 7. Effects “HR quality and framework conditions” | <ul style="list-style-type: none"> – Standardised online survey of research organisations (N=189 respondents from 136 organisations) – Synthesis of government research |
| 8. Context analysis | <ul style="list-style-type: none"> – Analysis of data on context gathered from modules 1 to 7 – Document analysis (including government research) |
| 9. Synthesis | <ul style="list-style-type: none"> – Two regional-language workshops with HR stakeholders on the need for optimisation – Synthesis of modules 1 to 8, conclusions and recommendations |

Source: See executive summary of the evaluation of the HRA (Widmer et al. 2019b: 4)

³⁴ Analysis of selected applications is being carried out separately from the evaluation and is presented in the report at hand.

7.2 Template for the assessment of an individual HRP's quality by the external specialist

Please use this template for your report on the assessment of the research quality of the human research project indicated below. The template aims at supporting a systematic assessment and having a meaningful basis for the comparative synthesis of the assessments of the different human research projects. We are aware that it might not be possible to cover all the aspects for all the categories listed and that the relevance of the categories and aspects provided might differ within and between the human research projects that you assess. The space needed to elaborate on the assessment of the categories might differ as well. Please note that there is additional space provided at the end of the form for any remarks that do not relate to any of the categories provided and for the overall impression of the research quality of the human research project.

Please write your report in English, German or French. Further information about the meaning of the different categories is provided in the annex.

| Project No. [] | | |
|-----------------------------|--|--|
| | | <p><i>Please provide, as far as possible, for each category S1-S4 and E1-E4 an assessment for the following aspects:</i></p> <p>Concept, conduct, application and decision</p> <p>Does the <i>conception</i> and preparation of the research project ensure the fulfilment of the criteria?</p> <p>Do the measures foreseen during the <i>conduct</i> of the project ensure the fulfilment of the criteria?</p> <p>Does the <i>application</i> contain the information necessary to assess the criteria? Is the information provided clear and comprehensible?</p> <p>Are the <i>decisions</i> well founded, comprehensible and fair?</p> |
| Scientific dimension | | |
| S1 | Relevance of the research question | |
| S2 | Suitability of the research design | |
| S3 | Professional qualification | |
| S4 | Availability of resources and responsibilities | |

| Project No. [] | | |
|--|---|--|
| <p>Please provide, as far as possible, for each category S1-S4 and E1-E4 an assessment for the following aspects:</p> <p>Concept, conduct, application and decision</p> <p>Does the <i>conception</i> and preparation of the research project ensure the fulfilment of the criteria?</p> <p>Do the measures foreseen during the <i>conduct</i> of the project ensure the fulfilment of the criteria?</p> <p>Does the <i>application</i> contain the information necessary to assess the criteria? Is the information provided clear and comprehensible?</p> <p>Are the <i>decisions</i> well founded, comprehensible and fair?</p> | | |
| Ethical dimension | | |
| E1 | Selection of the participants | |
| E2 | Information of the participants | |
| E3 | Protection and safety of the participants | |
| E4 | Respect for and involvement of the participants | |
| Additional remarks that do not fit in any of the categories provided above: | | |
| Overall impression: | | |

Annex: Overview of the human research quality criteria

| | | | | Aspects | | | |
|-----------------------------|----|--|---|--|---|---|--|
| | | | | Concept | Conduct | Application | Decision |
| Scientific dimension | S1 | <i>Relevance of the research question</i> | <ul style="list-style-type: none"> • Scope of research (research question in the area of research involving humans; necessity of research involving humans in answering the research question) • Discussion of relevant previous research (with human- or non-human subjects) or exploratory analyses • Argumentation for relevance of the research question | Does the conception and preparation of the research project ensure the fulfilment of the criteria? | Do the measures foreseen during the conduct of the project ensure the fulfilment of the criteria? | Does the application contain the information necessary to assess the criteria? Is the information provided clear and comprehensible? | Are the decisions well-founded, comprehensible and fair? |
| | S2 | <i>Suitability of the research design</i> | <ul style="list-style-type: none"> • Suitability of the design to answer the research question (definition and measurement of variables, blinding, population size and relevance, timing of measurements and endpoint, treatment and assignment thereof, statistical method) • Pre-defined, standardized approach of collection, documentation and quality control of data (incl. anticipation of possible sources of bias) | | | | |
| | S3 | <i>Professional qualification</i> | <ul style="list-style-type: none"> • Knowledge and experience of the principal investigator/project leader with regard to the subject investigated, project management and leadership | | | | |
| | S4 | <i>Availability of resources and responsibilities</i> | <ul style="list-style-type: none"> • Planning of necessary resources for the research project with respect to finances, personnel, time, rooms, equipment, liability insurance, availability of potential participants • Clarification of responsibilities | | | | |
| Ethical dimension: | E1 | <i>Selection of the participants</i> | <ul style="list-style-type: none"> • Suitability of inclusion and exclusion criteria to answer the research question • Fairness of selection (e.g. gender, children, other vulnerable groups, healthy volunteers vs patients) • Approach of recruiting participants incl. compensation of participants | | | | |
| | E2 | <i>Information of the participants</i> | <ul style="list-style-type: none"> • Design of the process of participant information and consent • Comprehensibility for laypersons in general and the group of participants in particular • Comprehensiveness (purpose of research and its procedures prior until after the project, potential risks, benefits and alternatives, rights and obligations, privacy policy) | | | | |
| | E3 | <i>Protection and safety of the participants</i> | <ul style="list-style-type: none"> • Provisions to minimize risks and burdens and to protect dignity, health and privacy of the participants: safety of products or devices used, dosage, radiation, protection and privacy measures for handling, access, analysis and storage of data and material (e.g. coding, only necessary information collected) | | | | |
| | E4 | <i>Respect for and involvement of the participants</i> | <ul style="list-style-type: none"> • Care during and after the project (handling of adverse or unexpected events, contact person, post-trial access to treatment) • Respect for participants (possibility of withdrawal, right to know and right not to know) • Availability of public information | | | | |

7.3 External specialists

Table A 2: External specialists: Names, institutional affiliation, functions and fields of expertise

| Name | Institution | | Country | Fields of Expertise |
|-----------------------|------------------------------|---|---------|---|
| | Name | Function | | |
| Teresa Anna Cantisani | Perugia Hospital | Professor, Director of the Department of Neurophysiopathology | Italy | Neurological sciences, systematic reviews |
| | Cochrane | Head of Cochrane Neurological Sciences Field | | |
| Josef Haas | Medical University of Graz | Professor, Department of Obstetrics and Gynaecology President Ethics Committee | Austria | Biometrics, statistics, medical ethics |
| Joerg Meerpohl | University of Freiburg | Professor, Head of the Institute for Evidence in Medicine | Germany | Epidemiology, paediatric haematology and oncology, systematic reviews |
| | Cochrane | Head of Cochrane Germany | | |
| Jürgen Zezula | Medical University of Vienna | Professor, Institute of Pharmacology Co-President Ethics Committee | Austria | Pharmacology, toxicology, medical ethics |